PPTA
Plasma Protein Therapeutics Association

Freezing and Storage of Source Plasma

Jim Viane, ZLB Plasma Services

FDA Workshop, 30 Aug – 1 Sep 2004.

PPTA
Plasma Protein Therapeutics Association

Topics

- Requirements for freezing and storage
- Factors affecting freezing
- Current industry practice
- Typical equipment needed
- Cost implications
- Safety concerns

CFR Requirements

- 21 CFR 640.76 ***Products stored or shipped at unacceptable temperatures.***
  - (a) Storage temperature. (1) Plasma for mfg. into injectable product that is exposed to temp. **greater than -20º C and less than +10ºC must be labeled "Source Plasma Salvaged".**
    - » ***Unless…***
  - (2) Source Plasma…exposed to one episode of storage temp. fluctuation warmer than **-20ºC and colder than -5ºC for not more than 72 hrs. is exempt from "Salvaged" labeling – provided that the plasma remains frozen solid.**
  - **Shipping at -5ºC or colder.**

EU Requirements

- EU Pharmacopoeia
  - Plasma for labile proteins: place at = -30º C within 24 hr.
  - Plasma for non-labile proteins: = -20ºC.
  - One excursion if = -20º C but, = -5ºC.
  - Shipping = -20ºC

PPTA
Plasma Protein Therapeutics Association

Factors Affecting Freezing

- Freezer configuration and size
- Environment (Tempe vs. Duluth)
- Freezer load (product)
- Center production volume (Infiltration)
- Heat exchange (time)

Example of Company Practice

- Source plasma frozen at: -20ºC or -30ºC

  Approx 8°C buffer for set point

  – To maintain -20ºC or colder = Alarm set point -28ºC
  – To maintain -30ºC or colder = Alarm set point -38 ºC
- Plasma placed in freezing chamber immediately after collection (usually 30 min). EP requires placement in -30ºC or colder within 24 hr (for recovery of labile proteins).
- Source plasma stored at -20ºC or colder (CFR and EP)
- Transport at -20ºC or colder to consignee or warehouse

Set Point Example

Design vs. alarm set point

For -30ºC : alarm set @ -38ºC, design set -45ºC

For -20ºC : alarm set @ -28ºC, design set -35ºC

Allows sufficient time for:

- Alarm co. to contact firm
- Firm to react and reach center
- Move product to secure location
- Repairs to be made without excursion

Equipment Requirements

Freezing = -20ºC

- 4” Urethane box
- Single stage system
- 6 HP Compressor
- Evaporator size
- Operating expense
- System cost ~ $30K

Freezing = -30ºC

- 5” Urethane box
- Two stage system
- 15 HP Compressor
- Evaporator size
- Operating expense 1.5 X
- System cost ~$100K

Flash Freezing

Freezing = -30ºC

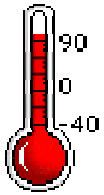
- 5” Urethane box
- Two stage system
- 15 HP Compressor
- Evaporator size
- Operating expense 1.5 X
- System cost $~100K

Flash Freezing = -55ºC

- Stand alone - 3 per center
- Two stage system
- 15 HP Compressor (each)
- Operating expense 3X
- System cost:
  - ~$90K installed (each)
  - ~$270K per center
- Additional storage freezers required

PPTA
Plasma Protein Therapeutics Association

Safety Concerns

Explanation	Freezer Temp	Approx. Wind speed	Approx. Equiv. temp	Risk Category	Suggested Max work period
Existing conditions	-30ºC	20 mph	- 55ºC	Increasing Danger[1]	30 min work – 3 breaks
Proposed rule on labeling and storage (2003)	-40ºC 	20 mph	-71ºC 	Great Danger[2]	Non-emergency work should cease
1 – Increasing Danger = Danger from freezing of exposed flesh in one min					
2 – Great Danger = Flesh may freeze within 30 seconds					

PPTA
Plasma Protein Therapeutics Association

Summary

- Current freezing requirements sufficient for manufacture of derivative products.
- Decreasing freezing/storage temperature 10ºC will require significant equipment upgrades
  - Replace with 2-stage equipment
  - Mechanically more complex and expensive
  - Requires specialized training for maintenance and repair
  - Parts not readily available
  - Replace existing 4” boxes with 5”
- Significant increase in cost to install, maintain and operate ultra-low equipment
- Increased cost to validate upgraded equipment
- Increased safety risk to center personnel